Rejections under 35 U.S.C. § 112

Claim 25 was rejected under 35 U.S.C. § 112, second paragraph as being indefinite because of the lack of antecedent basis for the phrase "heterologous nucleic acid." *See* Office Action, Paper No. 8, page 2, lines 10-15. Applicants have amended claim 25 to depend on claim 24, instead of the original dependency on claim 22. The original dependency on claim 22 was an inadvertent error because the antecedent basis for the phrase "heterologous nucleic acid" can be found in claim 24. Therefore, the amendment to change dependency provides antecedent basis and makes claim 25 definite under 35 U.S.C. § 112, second paragraph.

Claim 10 was rejected under 35 U.S.C. §112, first paragraph because the Office asserted that it relates to gene therapy and therefore is not enabled. *See* Office Action, Paper No. 8, page 2, line 21 through page 4, line 20. The Office acknowledged that claim 10 "does not recite explicitly the use of the claimed nucleic acid for therapy..." (page 3, lines 9-10), but still made the rejection because the claimed nucleic acid encodes a "therapeutic" protein, which, to the Office, indicates its use. Applicants have amended claim 10 to recite "wherein the heterologous nucleic acid sequence encodes a protein *associated with a disease*." (Emphasis added.) A protein associated with a disease does not imply a therapeutic use because there may be other uses, such as for research, for such a protein. Support for "a protein associated with a disease" can be found on page 14, line 15, of the specification, describing a "reporter gene or gene of other interest." Genes encoding proteins associated with a disease are "of other interest" than reporter genes. Because the amendment to claim 10 renders it enabled,

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applicants respectfully request that the rejection under 35 U.S.C. §112, first paragraph be withdrawn.

Claims 21-28 were also rejected under 35 U.S.C. §112, first paragraph because the Office asserted that they relate to gene therapy and therefore are not enabled. *See* Office Action, Paper No. 8, page 2, line 21, through page 7, line 16. Specifically, the claims were rejected because they include "both in vitro and in vivo uses," *see* Office Action, Paper No. 8, page 3, lines 5-6, and "encompass the specific ability to target cell types in vivo," *see* Office Action, Paper No. 8, page 4, lines 20-21. Applicants have amended independent claim 21, from which claims 22-28 depend, to recite a "process for inserting a nucleic acid of interest into the nucleus of a target cell, *in vitro* . . . ." The claimed process, performed *in vitro*, is demonstrated in the Examples, as acknowledged by the Office. *See* Office Action, Paper No. 8, page 7, lines 7-8 ("the applicants have provided only examples of in vitro experimentation"). The Examples provide support that the claims, as amended, are enabled. Because the claims now recite an *in vitro* process, applicants respectfully request that the rejection for lack of enablement of claims 21-28 be withdrawn.

Claims 33-40 were canceled and thus obviate the rejection under 35 U.S.C. § 112. *See* Office Action, Paper No. 8, page 2, line 21, through page 7, line 16.

Claims 21-32 were rejected under 35 U.S.C. §112 for lack of enablement for vectors other than HIV-based vectors, transduction of cells not within the host range of HIV-1 or VSV pseudotyped HIV-1, for targeting of cells *in vivo* or for nucleic acids which exceed the allowable insert size of an HIV-1 based vector. *See* Office Action, Paper No. 8, pages 7, line 18 through page 8, line 22 and page 9, line 14 through page 10, line

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2. Applicants have amended independent claims 21 and 29 to recite the nucleic acid depicted in Figure 5A, which is described on page 8, lines 3-7 of the specification. Therefore, these claims and the claims dependent on them are enabled by the specification.

Claims 21-32 were also rejected under 35 U.S.C. §112 because the Office suggested that "[c]ritical to the functioning of the invention as claimed is the generation of the triplex structure, which is based upon the reverse transcription of a nucleic acid. It is unclear and likely not possible that the triplex structure could be generated by other means." Office Action, Paper No. 8, page 9, lines 1-13. The Office asserted that the claims must include a reverse transcription step. Applicants have amended claims 21 and 29 to add the step "by reverse transcription" to modify "induce a three-stranded DNA structure." The description of Figure 6 provides support for this amendment, by providing that "[c]entral initiation and termination steps of HIV-1 reverse transcription creates a long plus strand DNA flap structure: the central DNA triplex." Specification, page 8, lines 20-22. With this amendment, claims 21 and 29, and claims depending on them, claims 22-28 and 30-32, respectively, are enabled under 35 U.S.C. §112. Applicants respectfully request that the Office withdraw its rejection.

Claim 13 was rejected under 35 U.S.C. §112, first paragraph because, allegedly, the vector claimed is not sufficiently described to enable one to make it. *See* Office Action, Paper No. 8, page 10, line 3 through page 11, line 15. In response, a Declaration by Danielle Berneman, Head of Patents & Inventions Office of the Institut Pasteur, is attached. The Declaration states that the deposit was made under the terms of the Budapest Treaty and that all restrictions imposed by the depositor on the

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availability to the public of the deposited material will be irrevocably removed upon the granting of a patent. Applicants submit that this conforms to the requirements of 37 C.F.R. § 1.801 - § 1.809.

35 U.S.C. § 102

Claims 1-4, 6-9, 11, 12, 14-25, 28-31, 41, and 43 were rejected under 35 U.S.C. § 102(b) as being anticipated by Akkina *et al.*, J. Virol., vol. 70, pages 2581-85 (1996) (hereinafter "Akkina"). *See* Office Action, Paper No. 8, page 11, line 16 through page 13, line 16. Specifically, the Office asserted that Akkina discloses a recombinant HIV-1 vector that meets all of the limitations of the claims. According to the Office, the vector in Akkina comprises the entire HIV-1 genome, except for the ENV gene, but including the cPPT and CTS regions and a heterologous gene. The Office further asserted that the disclosure in Akkina demonstrates that the vector is derived from a lentivirus or retrovirus, and that the vector can infect several cell types including hematopoeitic progenitor cells.

Applicants argue that Akkina does not anticipate the claimed invention as amended. Amended independent claims 1, 21, and 19 include reference to a nucleic acid as depicted in Figure 5A. Akkina does not recite a nucleic acid with only the elements shown in Figure 5A, but instead recites a nucleic acid including the entire HIV-1 genome, except for the ENV gene. Therefore, Akkina does not anticipate the amended claims. Applicants request that the rejection of independent claims 1, 21, 29, and the claims dependent on them, be with withdrawn.

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Claim 41 and 43 was also rejected under 35 U.S.C. §102(b). These claims have been canceled, thus obviating a response to this rejection. Applicants respectfully request that the rejection of these claims be withdrawn.

35 U.S.C. §103

Claims 10, 24-26, and 32 were rejected under 35 U.S.C. §103 (a) as being obvious in light of Akkina. *See* Office Action, Paper No. 8, page 13, line 17 through page 15, line 3. The Office asserted that expression of a therapeutic protein from the vector disclosed in Akkina would be obvious. Applicants argue that regardless of the expression of a therapeutic protein, Akkina does not render the claimed invention obvious. Akkina addresses only the *proteins* required for high efficiency gene transfer, not any of the elements of the HIV-1 *genome*. Akkina does not mention either the cPPT or CTS cis-acting regions of the HIV-1 genome. Neither does Akkina mention induction of a three-stranded DNA structure. There is no indication that either the cPPT, CTS, or a three-stranded DNA structure is necessary for the vectors disclosed in Akkina. Without an indication that these elements are necessary to the vectors demonstrated in Akkina, Akkina cannot render the claimed invention obvious.

Furthermore, Akkina states:

> In the present study, we showed that gene transfer into CD34+ cells can be increased severalfold over that for conventional vectors by pseudotyping the retroviral vector in a VSV-G envelope. The remarkable, higher level of efficiency achieved here is *likely due to the nature of the VSV-G in the envelope* which seems to interact with target cells via a universally present membrane component, possibly a phospholipid, in contrast to conventional, more restrictive, viral ligand-cell receptor interactions.

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(pages 2583, col. 2, line 35 through page 2584, col. 1, line 3, emphasis added), demonstrating that Akkina's focus is on the protein components of the HIV-1 based vector. This statement implies that it is only the protein components, and not the genomic components which produced the results shown in Akkina. Because "classical retroviral vector constructs" could have genomic regions, such as the cPPT and CTS elements, deleted, one skilled in the art would not have found it obvious from the disclosure in Akkina that anything more than the VSV-G protein is needed for high efficiency transfer. *See* Specification, page 27, lines 8-11 ("Classical retroviral vector constructs are replacement vectors in which the entire viral coding sequences between the LTRs are deleted and replaced by the sequences of interest. In the case of lentiviral vectors, this classical strategy leads to the deletion of the central cis-active sequences cPPT and CTS."). In contrast to Akkina, the present invention reveals that these genomic components lead to high efficiency gene transfer. By focusing on protein components of HIV-1 vectors, Akkina does not render the claimed invention obvious. Without support for the obviousness of all of the elements of the claims invention, the invention is not obvious *See* M.P.E.P. §2143 ("the prior art reference . . . must teach or suggest all the claim limitations.") Therefore, the rejection of claims 10, 24-26, and 32 should be withdrawn.

Claim 42 was also rejected under 35 U.S.C. §103(a). Claim 42 has been canceled, thus obviating a response to this rejection. Applicants respectfully request that the rejection of claim 42 be withdrawn.

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In view of the foregoing amendments and remarks, Applicants respectfully request the reconsideration and reexamination of this application and the timely allowance of the pending claims.

Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,
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Dated: April 30, 2002

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Appendix to the Amendment of April 30, 2002

Please amend the claims as follows:

1. (AMENDED) An isolated or purified nucleic acid [comprising] consisting of the sequence as depicted in Figure 5A, wherein at least one copy of the cPPT and CTS cis-acting regions of a retrovirus are present in the vector[, wherein] and the cPPT and CTS regions induce a three-stranded DNA structure.

10. (AMENDED) The nucleic acid of claim 9, wherein the heterologous nucleic acid sequence encodes a [therapeutic] protein associated with a disease.

21. (AMENDED) A process for inserting a nucleic acid of interest into the nucleus of a target cell, *in vitro*, said method comprising exposing an isolated or purified nucleic acid [comprising] as depicted in Figure 5A, wherein at least one copy of the cPPT and CTS cis-acting regions of a retrovirus are present in the vector and[, wherein] the cPPT and CTS regions induce a three-stranded DNA structure, by reverse transcription, to a target cell under conditions that permit uptake of the nucleic acid of interest into the target cell.

25. (AMENDED) The process of claim [22] 24, wherein the heterologous nucleic acid encodes a peptide, polypeptide, or protein.

29. (AMENDED) A process for expression a gene of interest *in vitro*, said process comprising

a) exposing target cells to an isolated or purified nucleic acid [comprising] as depicted in Figure 5A, wherein a gene of interest and at least one copy of the cPPT and CTS cis-acting regions of a retrovirus are present in the vector, and [, wherein] the cPPT and CTS regions induce a three-stranded DNA structure, by reverse transcription,

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under conditions that permit uptake of the nucleic acid into the target cell to create a recombinant cell, and

b) culturing the recombinant cell under conditions that permit at least part of the nucleic acid to be transferred to the nucleus of the recombinant cell and the gene of interest to be expressed.

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